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ORIGINAL ARTICLE

Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity

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Context: Body mass index (BMI) is widely used as a measure of overweight and obesity, but underestimates the prevalence of both conditions, defined as an excess of body fat.
Objective: We assessed the degree of misclassification on the diagnosis of obesity using BMI as compared with direct body fat percentage (BF%) determination and compared the cardiovascular and metabolic risk of non-obese and obese BMI-classified subjects with similar BF%.
Design: We performed a cross-sectional study.
Subjects: A total of 6123 (924 lean, 1637 overweight and 3562 obese classified according to BMI) Caucasian subjects (69% females), aged 18–80 years.
Methods: BMI, BF% determined by air displacement plethysmography and well-established blood markers of insulin sensitivity, lipid profile and cardiovascular risk were measured.
Results: We found that 29% of subjects classified as lean and 80% of individuals classified as overweight according to BMI had a BF% within the obesity range. Importantly, the levels of cardiometabolic risk factors, such as C-reactive protein, were higher in lean and overweight BMI-classified subjects with BF% within the obesity range (men 4.3 ± 9.2, women $4.9 \pm 19.5\,mg\,l^{-1}$) as well as in obese BMI-classified individuals (men 4.2 ± 5.5, women $5.1 \pm 13.2\,mg\,l^{-1}$) compared with lean volunteers with normal body fat amounts (men 0.9 ± 0.5, women $2.1 \pm 2.6\,mg\,l^{-1}$; $P<0.001$ for both genders).
Conclusion: Given the elevated concentrations of cardiometabolic risk factors reported herein in non-obese individuals according to BMI but obese based on body fat, the inclusion of body composition measurements together with morbidity evaluation in the routine medical practice both for the diagnosis and the decision-making for instauration of the most appropriate treatment of obesity is desirable.
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Keywords: BMI; adiposity; diagnosis; fat mass

Introduction

The prevalence of obesity is increasing dramatically worldwide.[1] Obesity is defined medically as a state of increased adipose tissue of sufficient magnitude to produce adverse health consequences and is associated with increased morbidity and mortality.[1] Surprisingly, obesity is a chronic disease that is often neglected and frequently not even thought of as a serious, life-threatening condition.[2,3]

Body mass index (BMI) is the most frequently used diagnostic tool in the current classification system of obesity. It has the advantage that a subject's height and weight are easy and inexpensive to measure. The World Health Organization (WHO), the US Preventive Services Task Force and the International Obesity Task Force define overweight as a BMI between 25.0 and $29.9\,kg\,m^{-2}$ and obesity as a BMI $\geqslant 30.0\,kg\,m^{-2}$.[4–7] These cutoffs are very useful in epidemiological studies[8] but in spite of its wide use BMI is

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only a surrogate measure of body fatness and does not provide an accurate measure of body composition.[8–21] Noteworthy, obesity is defined as an excess accumulation of body fat, with the amount of this excess fat actually being responsible for most obesity-associated health risks.[22]

Obesity increases the risk of cardiovascular diseases and type 2 diabetes[23,24] at the same time as imposing functional limitations in a number of subjects, which translate into a reduced quality of life as well as life expectancy.[18,25,26] Other anthropometric measures such as the waist circumference or the waist-to-hip ratio have been shown to better estimate the obesity-associated cardiovascular risk than BMI.[27,28] However, epidemiological studies analyzing the impact of the body fat percentage (BF%) on the levels of cardiometabolic risk factors are scarce.[29–31] It has been suggested that BF% is a better indicator of coronary heart disease risk than waist circumference.[32] Furthermore, BF% has been associated with all-cause mortality.[33–36] Therefore, it may be crucial to discriminate the clinical usefulness of measuring BF% to estimate the obesity-associated cardiometabolic risk.

Body composition analysis for determining BF% can be estimated by different techniques encompassing from skinfold measurement to magnetic resonance imaging.[37,38] Other frequently used methods for measuring body composition include bioelectrical impedance analysis and dual-energy X-ray absorptiometry. More accurate methods include underwater weighing and air displacement plethysmography (ADP). ADP is a validated and reproducible alternative to the gold standard hydrodensitometry.[39] It uses the pressure–volume relationship to estimate volume and density and has been shown to predict fat mass and fat-free mass more accurately than dual-energy X-ray absorptiometry and bioelectrical impedance analysis.[40] Body fat measured by ADP reportedly correlates better with cardiovascular risk factors than other anthropometric measures, but these findings, although relevant, have been obtained only in relatively small sample size studies.[41,42]

Therefore, we conducted a cross-sectional study with two aims: first, to estimate the degree of misclassification regarding the diagnosis of overweight and obesity by using BMI as compared with the direct determination of BF%. Second, to evaluate whether the cardiometabolic risk in non-obese individuals determined by BMI but classified as obese by BF% cutoff points is different to that of BMI-defined obese subjects with a similar BF%, thereby adding relevant information applicable for diagnostic and therapeutic decision-making.

Patients and methods

Study sample

We conducted a cross-sectional analysis of 6123 Caucasian subjects (4208 females/1915 males), aged 18–80 years including patients visiting the Departments of Endocrinology and Surgery of the University Clinic of Navarra for weight loss treatment as well as hospital and University staff undergoing an annual routine health check-up between January 2005 and December 2009. All patients were weight-stable for the previous 3 months. A subset of 3051 subjects (2213 females/838 males) was included in the analysis designed to compare the cardiovascular and metabolic risk between non-obese and obese individuals classified by BMI with a similar body fat content. The study included as the reference group the subjects classified as lean by both BMI and BF% (560 women and 96 men), and compared it to those classified as non-obese by BMI ($<30.0\,kg\,m^{-2}$) but obese by BF% (1208 women and 371 men) as well as to a BF%-matched group of individuals classified as obese by both BMI and BF% (445 women and 371 men). Presence of metabolic syndrome was determined following already described criteria.[43] The experimental design was approved, from an ethical and scientific standpoint, by the Hospital's Ethical Committee responsible for research and informed consent was obtained from all subjects.

Anthropometric measurements

The anthropometric and body composition determinations as well as the blood extraction were performed on a single day. Height was measured to the nearest 0.1 cm with a Holtain stadiometer (Holtain Ltd, Crymych, UK), whereas body weight was measured with the ADP calibrated electronic scale to the nearest 0.1 kg with subjects wearing a swimming suit and cap. BMI was calculated as weight in kg divided by the square of height in meters. Waist circumference was measured at the midpoint between the iliac crest and the rib cage on the midaxillary line. Hip circumference was measured at the point yielding the maximum circumference over the buttocks to the nearest 1 cm. Blood pressure was measured after a 15-min rest in the semi-sitting position with a sphygmomanometer. Blood pressure was determined at least three times at the right upper arm and the mean was used in the analyses.

Body composition

Body density was estimated by ADP (Bod-Pod, Life Measurements, Concord, CA, USA). Data for estimation of body fat by this plethysmographic method have been reported to agree closely with the traditional gold standard hydrodensitometry underwater weighing.[39,40] Percentage of body fat was estimated from body density using the Siri equation.[44] Cutoff points for BF% used for defining overweight (20.1–24.9% for men and 30.1–34.9% for women) and obesity ($\geqslant$25.0% for men and $\geqslant$35.0% for women) are those most frequently used in the literature.[15,21,42,45–48]

Laboratory procedures

Blood samples were collected after an overnight fast in the morning to avoid potential confounding influences due to

hormonal rhythmicity. Plasma glucose and insulin was analyzed as previously described.[49,50] An indirect measure of insulin resistance was calculated by using the homeostatic model assessment.[51] Total cholesterol and triglyceride concentrations were determined by enzymatic spectrophotometric methods (Roche, Basel, Switzerland). High-density lipoprotein (HDL-cholesterol) was quantified by a colorimetric method in a Beckman Synchron CX analyzer (Beckman Instruments, Ltd, Bucks, UK). Low-density lipoprotein (low-density lipoprotein-cholesterol) was calculated by the Friedewald formula.

Uric acid and alanine aminotransferase (ALT) were measured by enzymatic tests (Roche) in an automated analyzer (Roche/Hitachi Modular P800). Fibrinogen concentrations were determined according to the method of Clauss using a commercially available kit (Hemoliance, Instrumentation Laboratory, Barcelona, Spain). Measurement of von Willebrand factor (vWF) antigen was performed by a microlatex immunoassay (Diagnostica Stago, Inc., Parsippany, NJ, USA). A standard curve was prepared with a universal reference (NISBC 91/666) and the results were expressed as percentage of the standard. Intra-and inter-assay coefficients of variation were 4.0% and 8.0%, respectively. High-sensitivity C-reactive protein (CRP) was measured using the Tina-quant CRP (Latex) ultrasensitive assay (Roche). Leptin was quantified by a double-antibody RIA method (Linco Research, Inc., St Charles, MO, USA); intra-and inter-assay coefficients of variation were 5.0% and 4.5%, respectively.

Statistical analysis

Data are presented as mean ± s.d. Differences between groups were analyzed by analysis of variance followed by Scheffé's tests or analysis of covariance. CRP and leptin concentrations were logarithmically transformed, because of their non-normal distribution. The distribution of other variables was adequate for the application of parametric tests. Correlations between two variables were computed by Spearman (ρ) correlation coefficient. Analyses of receiver operating characteristic curves were used to evaluate the overall performance of BMI to detect obesity defined by BF%. Sensitivity and specificity were calculated and used to identify the best gender-specific BMI cutoffs for detecting BF%-defined obesity. General linear model analysis was used to create a predictive equation for BF% (dependent variable) including BMI, sex, age and their interactions as the independent variables. The calculations were performed using the SPSS version 15.0.1 (SPSS, Chicago, IL, USA). A *P*-value lower than 0.05 was considered statistically significant.

Results

In the sample as a whole, BMI and BF% showed a strong correlation ($\rho = 0.71$; $P < 0.0001$), which was stronger after stratification by gender; ($\rho = 0.78$; $P < 0.0001$ for males; $\rho = 0.87$; $P < 0.0001$ for females) (Figure 1). As expected women exhibited a higher BF% for a given BMI than men. To identify a predictive equation of BF% a stepwise linear regression using BF% determined by ADP as the outcome variable and sex, age, BMI, BMI square and the interactions between the linear BMI and quadratic BMI with age and gender was performed. The equation that better predicts BF% is as follows:

$$BF\% = -44.988 + (0.503 \times age) + (10.689 \times gender) + (3.172 \times BMI) - (0.026 \times BMI^2) + (0.181 \times BMI \times gender) - (0.02 \times BMI \times age) - (0.005 \times BMI^2 \times gender) + (0.00021 \times BMI^2 \times age)$$

wherein male = 0 and female = 1 for gender. The equation includes both a linear and a quadratic BMI component. This model explains 79% of the variability in BF% with a standard error of the estimate of 4.7%. The correlation coefficient of measured versus predicted BF% values with the equation was $\rho = 0.88$ ($P < 0.0001$).

Our study included 924 lean (15%), 1637 overweight (27%) and 3562 (58%) obese subjects classified according to BMI. Figure 2 shows the classification of the subjects as lean, overweight or obese according to either BMI or BF%. Striking differences were observed depending on the criterion used. According to the actual BF% values, 29% of the lean individuals following the established BMI criteria were obese given their BF%, whereas only 0.2% considered obese by BMI was in reality lean according to BF%. Furthermore, 80% of the BMI overweight-classified individuals were actually obese considering their BF%. This misclassification was higher for women (30% obese by BF% classified as lean by BMI and 84% obese by BF% classified as overweight according to BMI) than for men (25% obese by BF% classified as lean by BMI and 71% obese by BF% classified as overweight according to BMI). The misclassification becomes also evident in the scatter-plots showing BMI vs BF% with the cutoff points marked by reference lines for women and men (Figure 1).

Receiver operating characteristic curves were elaborated (Supplementary Figure 1) to analyze the performance of BMI to detect obesity according to BF% ($\geqslant$25.0% in men and $\geqslant$35.0% in women). The recommended BMI cutoff of $\geqslant 30.0\,kg\,m^{-2}$ has an excellent specificity (89% in men and 98% in women) but has a poor sensitivity (77% in men and 65% in women). In men, the area under the curve was 0.91, with the best BMI cutoff to detect obesity according to BF% being $29.0\,kg\,m^{-2}$, which resulted in a sensitivity (true-positive rate) of 84% and a specificity (true-negative rate) of 85%. In women, the area under the curve was 0.94 and the best BMI cutoff identified was $26.8\,kg\,m^{-2}$, which resulted in a sensitivity of 85% and a specificity of 88%.

To evaluate the impact of the observed misclassification on the potential underestimation of the obesity-associated cardiometabolic risk, several risk factors were compared between subjects with a similar BF% within the obesity range but classified either as non-obese (NOOB) or obese (OBOB) by BMI criteria (the subjects included can be observed in Figure 3). According to these matching criteria,

although men from the OBOB group exhibited a BMI within the obesity range and those of the NOOB group were classified either as lean or overweight by BMI criteria they both had similar BF% (BF% ~31%; $P=0.269$), which were well within the obesity range (Table 1). Both groups exhibited higher waist and hip circumferences and waist-to-hip ratio ($P<0.001$ for all) as well as systolic blood pressure (SBP) ($P<0.001$) and diastolic blood pressure (DBP) ($P<0.001$) than the reference lean group, being higher in the OBOB group ($P<0.001$, $P<0.01$ and $P<0.05$ for waist, hip, waist-to-hip ratio, SBP and DBP, respectively) as compared to NOOB. Although SBP and DBP were significantly higher in

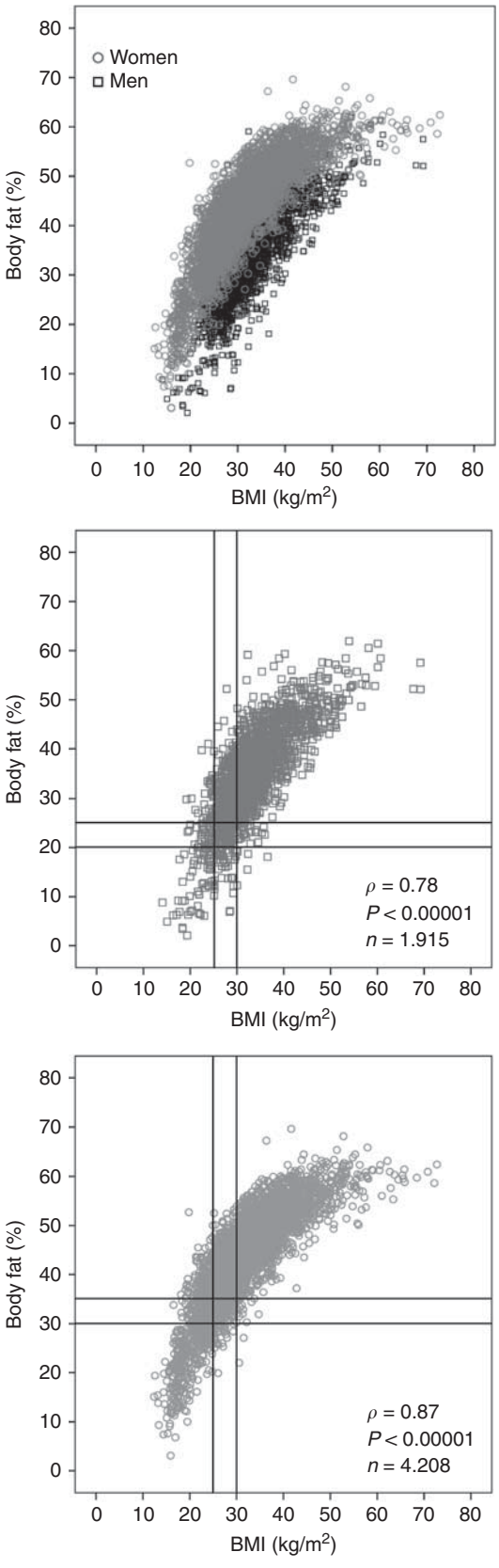

Figure 1 Correlation between body mass index and BF% for the whole sample and stratified by gender. Top: total sample of 6123 subjects. Center: men ($n=1915$). Bottom: women ($n=4208$). Vertical lines indicate cutoffs for defining overweight and obesity according to BMI (25.0 and 30.0 kg m^{-2}, respectively) and horizontal lines indicate cutoffs for defining overweight and obesity according to BF% (20.0 and 25.0% in men and 30.0 and 35.0% in women, respectively).

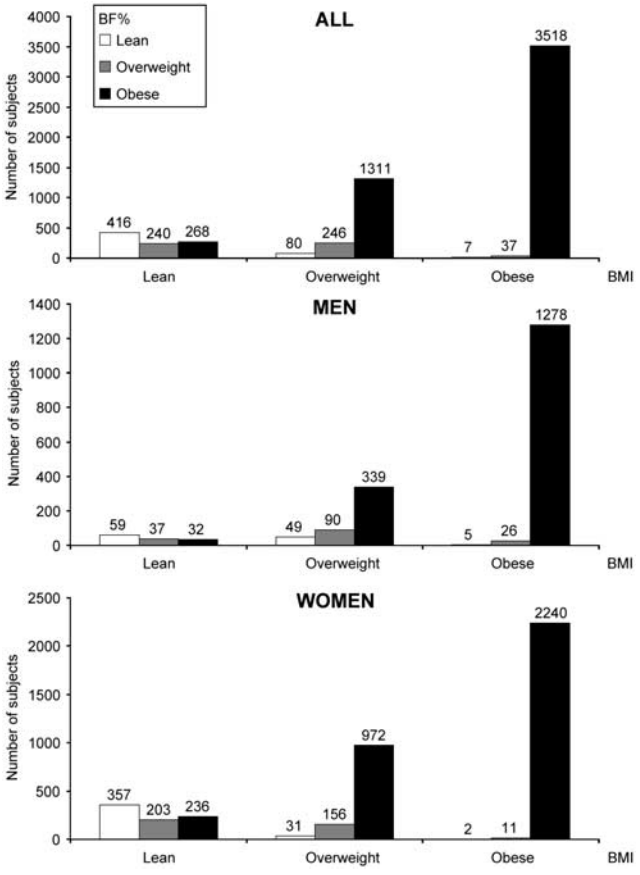

Figure 2 Classification of subjects as lean, overweight or obese according to BMI or BF%. Overweight was defined as BF% between 20.1–24.9% in men or between 30.1–34.9% in women, or BMI between 25.0–29.9 kg m^{-2}. Obesity was defined as BF% $\geqslant$25.0% in men or $\geqslant$35.0% in women, or BMI $\geqslant$30.0 kg m^{-2}.

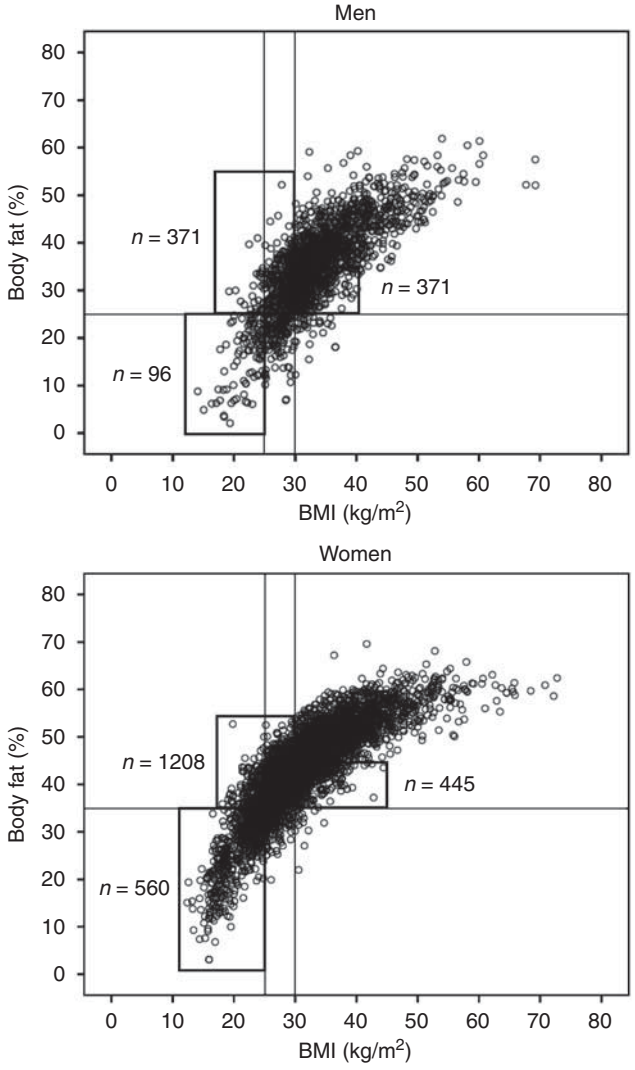

Figure 3 Scatter plots showing the selected subjects included in the comparison showed in Table 1. The boxes indicate the selected individuals. Obese subjects according to BF% in the upper boxes in each figure were matched by BF%. Number of individuals is indicated. Vertical lines indicate cutoffs for defining overweight and obesity according to BMI (25.0 and 30.0 kg m^{-2}, respectively) and horizontal lines indicate cutoffs for defining obesity according to BF% (25.0% in men and 35.0% in women, respectively).

NOOB and OBOB groups, they remained within the normal range. Plasma glucose levels were significantly higher in the NOOB group as compared with leans ($P<0.05$), exhibiting a tendency towards significance in the OBOB group ($P=0.081$). Insulin concentrations were elevated in both obese groups ($P<0.05$, and $P<0.001$ for NOOB and OBOB as compared with leans, respectively), being higher in the OBOB ($P<0.01$, as compared with NOOB), with only this group exhibiting statistically significant higher homeostatic model assessment values ($P<0.01$ and $P=0.050$ vs lean and NOOB, respectively). The lipid profile was overall similarly higher in both the NOOB and OBOB obese groups as compared with the lean volunteers with the exception of total cholesterol that was significantly increased only in the NOOB subjects ($P<0.05$) and HDL cholesterol levels that were decreased in both obese groups ($P<0.001$) and further reduced in the OBOB ($P<0.001$). Interestingly, the markers of inflammation, fibrinogen and CRP, were significantly higher in both obese groups ($P<0.05$ and $P<0.001$, respectively) showing no differences between them. In women, as a general tendency almost all the variables analyzed were significantly higher in both obese groups (BF% $\sim$41%; $P=0.104$), being higher in the OBOB as compared with the NOOB group. Analogously to what was observed in men, CRP concentrations were higher in the female NOOB and OBOB groups as compared with leans ($P<0.001$) showing no differences between them, thereby indicating a low-grade chronic inflammation in both obese (NOOB and OBOB) groups regardless of gender. As subjects in the OBOB groups from both genders exhibited a higher waist than those from the NOOB groups, we performed a reanalysis between these two groups adjusting for waist circumference and age. Many of the differences between NOOB and OBOB groups were attributable to waist circumference as DBP, insulin concentrations, uric acid levels and leptin concentrations in men and SBP, DBP, triglyceride levels, low-density lipoprotein, uric acid concentrations and ALT in women showed no significant differences between NOOB and OBOB after adjusting for waist and age.

In addition, we also analyzed the percentage of individuals with normal waist circumference (below 102 and 88 cm in men and women, respectively) with increased cardiometabolic risk factors finding that 5.1, 2.8, 3.8, 4.0 and 11.2% of subjects had elevated fasting plasma glucose ($\geqslant$100 mg dl^{-1}), triglycerides ($\geqslant$150 mg dl^{-1}), CRP ($>$3 mg l^{-1}) concentrations, SBP ($\geqslant$140 mm Hg) and reduced HDL cholesterol concentrations ($<$40 mg dl^{-1} in men and $<$50 mg dl^{-1} in women), respectively. When the analysis included subjects with BMI below 30 kg m^{-2}, we found that 7.0, 4.3, 5.2, 7.0 and 14.6% of subjects exhibited elevated fasting plasma glucose, triglycerides, CRP concentrations, SBP and reduced HDL cholesterol concentrations, respectively. However, when the same analysis was performed in individuals with a BF% below the cutoff considered as obesity (below 25.0 and 35.0% in men and women, respectively) only 1.7, 0.8, 1.6, 1.4, and 5.4% of subjects had elevated fasting plasma glucose, triglycerides, CRP concentrations, SBP and reduced HDL cholesterol concentrations, respectively (data not shown). In addition, we also analyzed the advantages of better diagnosing the metabolic syndrome in the obese population with either BF% or BMI. When the presence of the metabolic syndrome was evaluated in the obese population (according to BMI), 77% of patients with the syndrome was detected, whereas 23% of them were undiagnosed. However, when the presence of the metabolic syndrome was measured in the obese population (according to BF%), 96% of patients with the syndrome was diagnosed.

Table 1 Characteristics of subgroups of individuals separated as lean or obese according to BMI and body fat criteria

	Men				*Women*			
	Lean (BMI and BF%) (n = 96)	*Non-obese-BMI/Obese BF% NOOB (n = 371)*	*Obese-BMI/Obese BF% OBOB (n = 371)*	P	*Lean (BMI and BF%) (n = 560)*	*Non-obese-BMI/obese BF% NOOB (n = 1208)*	*Obese-BMI/obese BF% oBOB (n = 445)*	P
Age (years)	38.6 ± 12.6	47.9 ± 13.0*	45.1 ± 12.5*	<0.001	35.5 ± 13.3	44.8 ± 13.6*	42.5 ± 12.7*, **	<0.001
BMI (kg m^{-2})	22.0 ± 2.4	27.8 ± 1.8*	32.8 ± 2.3*, **	<0.001	20.9 ± 2.9	26.8 ± 2.2*	32.8 ± 2.4*, **	<0.001
Body fat (%)	16.7 ± 6.1	31.5 ± 4.2*	31.0 ± 2.4*	<0.001	26.3 ± 6.5	40.9 ± 3.7*	41.4 ± 2.2*	<0.001
Waist (cm)	83 ± 8	99 ± 6*	108 ± 7*, **	<0.001	72 ± 8	87 ± 8*	100 ± 8*, **	<0.001
Hip (cm)	92 ± 5	102 ± 5*	109 ± 6*, **	<0.001	91 ± 8	103 ± 6*	111 ± 7*, **	<0.001
WHR	0.90 ± 0.06	0.97 ± 0.05*	0.99 ± 0.05*, **	<0.001	0.79 ± 0.07	0.85 ± 0.08*	0.89 ± 0.08*, **	<0.001
SBP (mm Hg)	111 ± 12	121 ± 14*	125 ± 14*, **	<0.001	103 ± 14	113 ± 14*	117 ± 15*, **	<0.001
DBP (mm Hg)	69 ± 8	75 ± 8*	77 ± 9*, **	<0.001	65 ± 9	71 ± 8*	73 ± 9*, **	<0.001
Glucose (mmol l^{-1})	5.16 ± 1.05	5.77 ± 1.72*	5.72 ± 1.55	<0.05	4.83 ± 0.56	5.00 ± 0.61*	5.16 ± 1.17*, **	<0.001
Insulin (pmol l^{-1})	50 ± 31	78 ± 52*	96 ± 59*, **	<0.001	43 ± 22	60 ± 63*	94 ± 75*, **	<0.001
HOMA	1.78 ± 1.58	2.80 ± 2.53	3.47 ± 2.78*	<0.01	1.32 ± 0.70	1.91 ± 2.01*	2.99 ± 2.83*, **	<0.001
Triglycerides (mmol l^{-1})	0.98 ± 0.49	1.58 ± 1.80*	1.75 ± 1.37*	<0.01	0.79 ± 0.29	1.02 ± 0.64	1.42 ± 3.71*, **	0.001
Cholesterol (mmol l^{-1})	4.6 ± 1.0	5.0 ± 1.2*	4.9 ± 1.1	<0.05	4.8 ± 0.9	5.1 ± 1.1*	4.8 ± 1.4**	<0.05
LDL cholesterol (mmol l^{-1})	2.7 ± 0.9	3.1 ± 0.9*	3.1 ± 1.0*	<0.05	2.8 ± 0.8	3.1 ± 1.0*	2.9 ± 1.0**	<0.05
HDL cholesterol (mmol l^{-1})	1.4 ± 0.5	1.2 ± 0.3*	1.1 ± 0.3*, **	<0.001	1.6 ± 0.4	1.6 ± 0.4*	1.3 ± 0.4*, **	<0.001
Uric acid (μmol l^{-1})	324 ± 72	342 ± 66	378 ± 72*, **	<0.001	228 ± 48	252 ± 54*	270 ± 60*, **	<0.001
ALT (UI l^{-1})	21 ± 15	22 ± 12	29 ± 17*, **	<0.001	15 ± 10	17 ± 12	20 ± 20*, **	<0.001
Fibrinogen (g l^{-1})	2.48 ± 0.65	3.11 ± 0.70*	3.08 ± 0.69*	<0.05	3.29 ± 0.75	3.39 ± 0.72	3.39 ± 0.70	0.577
vWF (%)	100 ± 23	97 ± 23	120 ± 44*	<0.05	118 ± 33	124 ± 57	110 ± 51	0.057
CRP (mg l^{-1})	0.9 ± 0.5	4.3 ± 9.2*	4.2 ± 5.5*	<0.001	2.1 ± 2.6	4.9 ± 19.5*	5.1 ± 13.2*	<0.001
Leptin (ng ml^{-1})	4.0 ± 2.0	11.2 ± 7.2*	15.7 ± 11.6*, **	<0.001	14.3 ± 10.4	26.8 ± 16.9*	34.4 ± 19.4*, **	<0.001

Abbreviations: ALT, alanine aminotransferase; BF%, body fat percentage; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; SBP, systolic blood pressure; vWF, von Willebrand factor; WHR, waist-to-hip ratio. Data are presented as mean ± s.d. Differences between groups were analyzed by analysis of variance followed by Scheffé's tests. *$P<0.05$ vs lean. **$P<0.05$ vs non-obese-BMI/obese %BF. CRP, vWF and leptin concentrations were logarithmically transformed for statistical analysis.

Discussion

Obesity represents a body fat excess, with the amount of this excess correlating with comorbidity development.[17,22] We found that 29% of subjects classified as lean according to BMI, that is, with a BMI <25.0 kg m^{-2}, and 80% of subjects classified as overweight according to actual BMI, that is, with a BMI $\geqslant 25.0$ kg m^{-2} and <30.0 kg m^{-2}, had a BF% well within the obesity range. However, only 0.2 and 1.0% of the subjects with a BF% in the lean or overweight range, respectively, was misclassified as obese according to the BMI value. This datum shows that BMI, although being an extremely valuable tool for epidemiological studies, underestimates BF% especially in the overweight category.[3,17] Thus, our study clearly indicates that there is a high degree of misclassification in the diagnosis of obesity in clinical practice, which results in the underdiagnosis of patients at risk and, therefore, missed opportunities to treat this life-threatening condition. The information derived from receiver operation characteristics analyses suggests that the actual cutoff points that more accurately diagnose obesity are 29.0 kg m^{-2} in men and 27.0 kg m^{-2} in women.

In spite of the fact that BF% and obesity increase the risk of cardiovascular diseases and type 2 diabetes,[23,24] large epidemiological studies analyzing the relation between BF% and circulating concentrations of cardiometabolic risk markers are scarce. For the first time, our study provides evidence in a large sample that the levels of cardiometabolic risk factors are similarly higher in lean or overweight BMI-classified subjects with body fat percentages within the obesity range than in obese BMI-classified individuals with matched BF%. Our data show that non-obese subjects by the BMI criterion but obese by BF% exhibit higher blood pressure, glucose, insulin, triglycerides, low-density lipoprotein, fibrinogen and CRP concentrations (see Table 1), with many of them above the cutoff points established for predicting cardiovascular or metabolic risk. For instance, this group of non-obese individuals as defined by BMI but obese according to BF% already exhibit mean fasting glucose levels above 5.6 mmol l^{-1}, which is currently considered as IGT, a homeostatic model assessment index over 2.61, which is the cutoff point indicating insulin resistance,[47,51] and CRP plasma concentrations above 3.0 mg l^{-1}, which is the lower limit of the higher risk range.[52] Furthermore, our data provide scientific explanation to the finding that body composition may help to understand the cardiovascular risk in 'normal-weight' subjects with high adiposity.[29,53,54]

The few studies analyzing the influence of BF% on cardiometabolic risk factor levels have been predominantly aimed to compare the influence of body fat distribution than to analyze the effect of increased adiposity itself[32,47,55,56] or have been performed in volunteers with BMI values within

the lean range.[20] In this sense, BF% shows lower,[56] similar,[47] or higher[57] correlation with metabolic risk factors than central adiposity measures, but has been recently suggested as a better indicator of coronary heart disease risk than waist circumference.[32] The present study emphasizes that anthropometric indicators of body fat distribution such as waist circumference or waist-to-hip ratio are important when evaluating the risk of a subject regardless of its body weight. However, our data further indicate that the actual body fat amount is also having a key role in the increased cardiometabolic risk. In this sense, the use of BF% cutoff points to diagnose obesity allows to detect more individuals with an increased cardiometabolic risk than simple application of the waist circumference classification criteria. In addition, our data suggest that with the new proposed cutoff points a lower number of patients with the metabolic syndrome would be undiagnosed.

In the same way as a progressive decrease in the cutoff points for the diagnosis of hypertension or circulating cholesterol concentrations has been observed in past years, our findings highlight that a reappraisal of the cutoffs to diagnose overweight and obesity may be considered. This is particularly important based on the pathophysiological implications that increased adiposity has in the context of normal- or over-weight. Although BMI is widely used as a proxy measure of body fat, it does not provide information on body composition as evidenced herein. The present study provides evidence for the existence of a similar adverse cardiometabolic risk factor profile already in subjects with a BMI $< 30.0\,kg\,m^{-2}$ but highly increased adiposity compared with obese patients.

One potential limitation of our study pertains to the generalizability to other populations. This study was conducted in Caucasian subjects and would need to be extended to other populations to determine race-specific differences, as regarding BF% ranges for a given BMI and if the significant correlations to the cardiometabolic risk factors are (i) maintained, and (ii) if so, establish to which degree.[9,10,58] Another potential limitation of the present study is that smoking and medication were generally not available. Accordingly, we could not adjust for the potential confounding effects of these variables. However, we consider that the relatively large sample size may compensate this limitation.

In summary, the use of BMI for obesity diagnosis in clinical practice underestimates the true prevalence of this life-threatening condition given its association with the elevation of well-recognized cardiometabolic risk factors. Our data indicate that a relevant number of obese patients at risk are being underdiagnosed, and, therefore, opportunities for adequate treatment instauration and comorbidity assessment are being missed. The actual cutoff points that more accurately diagnose obesity are $29.0\,kg\,m^{-2}$ in men and $27.0\,kg\,m^{-2}$ in women. In this sense, the inclusion of body composition measurements together with morbidity evaluation in the routine medical practice both for the diagnosis and the decision making for instauration of the most appropriate treatment of obesity is desirable.

Conflict of interest

The authors declare no conflict of interest.

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